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Candidacy for heart transplantation in adult congenital heart disease patients: A cohort study

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ABSTRACT

Objective: The object of the present study is to evaluate factors precluding heart transplantation (HTx) in adult congenital heart disease patients (ACHD) with end-stage heart failure (HF) referred for HTx evaluation.
Methods: This retrospective cohort study enrolled consecutive ACHD patients considered for HTx in our institution between 2014 and 2020 and patients receiving HTx between 2001 and 2013. HTx refusal due to poor candidacy status for excess risk of mortality after transplantation served as the main study outcome.
Results: Between 2014 and 2020, 46 ACHD patients were evaluated for HTx, 14 ACHD patients underwent HTx between 2001 and 2013 (final sample size 60 patients). We compared clinical, anatomical and demographic data of 41 patients suitable for transplantation with 15 patients refused after screening (excluding 4 patients with ongoing screening). Risk factors for refusal were: multiple high risk features (odds ratio [OR]: 3.6; 95% confidence interval [CI]: 1.1 to 12.9; p 0.048); anatomical factors (OR: 14.5; 95% CI: 3.1 to 68.4; p 0.001), out-of-center ACHD/HTx program referral (OR: 5.3; 95% CI: 1.5 to 19.0; p 0.01). HTx refusal identifies a high risk ACHD patient subgroup (hazard ratio for overall mortality: 3.1; 95% CI: 1.1 to 8.3; p 0.02).
Conclusions: In our study risk factors for refusal from HTx are adverse anatomical features, multiple conventional HTx high risk factors and out-of-center referral. ACHD patients refused from HTx present shorter time to death. Efforts to increase HTx candidacy are strongly necessary for this growing population.

1. Introduction

Life expectancy of patients with congenital heart disease (CHD) has increased in the last few decades and nowadays the number of adults with CHD (ACHD) in western countries exceeds that of children [1,2].

ACHD patients experience several complications affecting life expectancy [3]. Cardiovascular mortality in these patients is significant and heart failure (HF) is the leading cause of death accounting for 26% of deaths [4]. End-stage HF is the main indication for orthotopic heart transplantation (HTx) and is an important therapeutic option for a selected group of ACHD patients [5].

HTx improves the prognosis and quality of life in ACHD patients with end-stage HF. Although higher peri-transplant mortality is reported in this patient population, conditional mortality after the first year of transplant is higher than in patients with non-congenital cardiac disease (mean survival of 15 years versus 12 years respectively) [6,7].

HTx candidacy evaluation in ACHD is challenging due to multiple risk factors (previous sternotomies, long-lasting cardiac dysfunction, cyanosis, unfavorable anatomy, end-organ damage, sensitization and pulmonary hypertension) [7–9]. Because the continued expansion of ACHD population needing HTx and the limited number of donors a careful patient selection is required but patient selection and proper HTx

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timing remain a sensitive and unresolved issue in this field. A delay in evaluation for heart transplant can lead to complications (such as HF worsening, organ dysfunctions, progressive pulmonary vascular disease) that can compromise HTx suitability and increase early mortality after HTx [10].

Understanding current practice in ACHD HTx referral and evaluation is required to improve listing timing, to enhance patient selection and to increase patient and graft survival.

This retrospective cohort study reports ACHD HTx referral pattern and following candidacy evaluation in a tertiary referral center for HTx-ACHD of a large Italian academic medical center to identify risk factors associated to HTx refusal for excess risk of mortality after transplantation.

2. Methods

2.1. Data collection

All consecutive ACHD patients evaluated from January 2014 to December 2020 at ACHD Program of IRCCS Azienda Ospedaliera Universitaria di Bologna (Italy) and discussed at the multidisciplinary meeting (MDM) for HTx candidacy evaluation, were included in this retrospective single-center cohort study. Patients aged over 18 and with CHD transplanted in our Center between 2001 and 2013 were also included (Fig. 1).

Patients were categorized into three groups due to anatomical conditions:

1) systemic left ventricle (SLV), with concordant ventriculo-arterial and atrio-ventricular connections, two balanced ventricles with SLV and biventricular circulation;
2) systemic right ventricle (SRV), ventriculo-arterial and/or atrio-ventricular discordance, two balanced ventricles with SRV and biventricular circulation;
3) single ventricle (SV), patients with anatomically unbalanced ventricles/ventricular hypoplasia or absence, inability to restore a biventricular circulation (such as atrial isomerism) leading to a physiological univentricular circulation (including classic/modified Glenn or Fontan circulation).

Demographic characteristics, clinical data, laboratory and radiological findings, cardiac right catheterization data, medical treatments and meeting results were collected from electronic medical records and outpatients visits. Data lock for follow-up data was June 2021.

This study was approved by the institutional review board of Azienda Ospedaliera Universitaria di Bologna (Italy).

Patient and Public Involvement: For this research patients and the public were not involved in study design, data collection and interpretation or data dissemination.

2.2. Multidisciplinary meeting and transplant screening

Decision to consider patient for HTx was clinically triggered by an experienced ACHD physician. Institutional protocol mandates for each patient a multidisciplinary ACHD Heart Team evaluation with experienced and dedicated cardiologists, cardiac surgeons, anesthesiologist

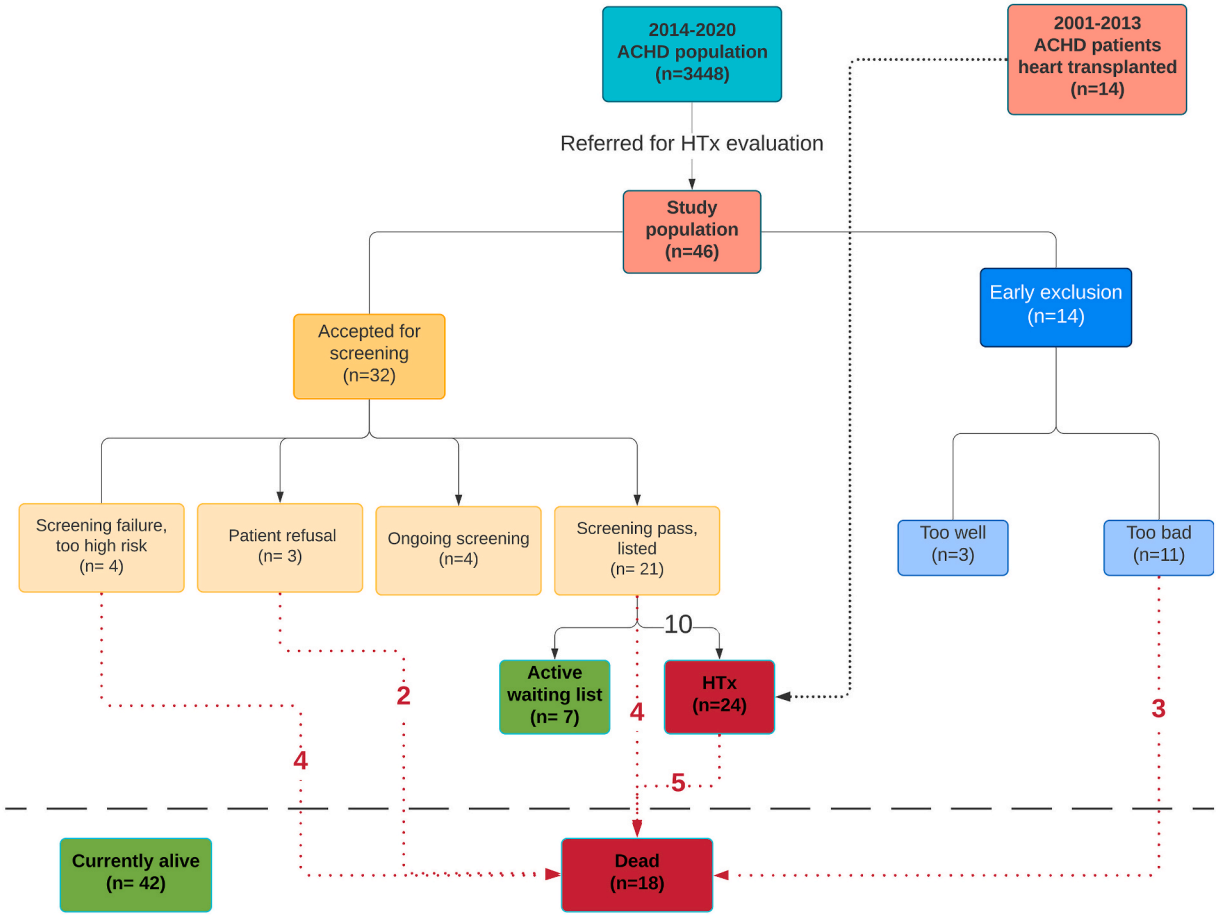

Fig. 1. Patient's pre-transplant evaluation and outcomes. The flowchart shows the population enrollment and outcomes. Since 2014, 46 patients were discussed to HTx screening: 11 were excluded from the multidisciplinary meeting because considered "too bad", 32 were accepted for screening. Fourteen additional ACHD patients underwent transplantation in the period between 2001 and 2013. ACHD = adult with congenital heart disease; HTx = Heart transplant.

Table 1
Clinical and demographic features of the overall study population and stratified based on ventricular morphology.

Variable	Overall cohort (n = 60)	Single ventricle (n = 27)	Systemic LV (n = 19)	Systemic RV (n = 14)	p-value
Age, years	35 (26–46)	29 (26–40)	34 (27–46)	43 (30–48)	0.2
Weight, kg	62 (52–73)	57.5 (48–68.5)	62 (51–73)	70.5 (62–76)	0.2
Height, cm	169 ± 10	170 ± 10	168 ± 10	169 ± 11	0.93
BSA, m^2	1.8 (1.5–1.9)	1.7 (1.5–1.8)	1.7 (1.5–1.9)	1.8 (1.8–1.9)	0.18
NYHA III/IV, n (%)	29 (48%)	12 (44%)	11 (58%)	6 (43%)	0.67
History of syncope, n (%)	9 (15%)	2 (7%)	5 (22%)	2 (14%)	0.24
Primary cardiac anatomy, n (%)					–
Unspecified SV	18 (30%)	18 (67%)	0 (0%)	0 (0%)	
D-TGA/ccTGA	18 (30%)	3 (11%)	2 (10.5%)	13 (93%)	
Tricuspid valve disease	5 (8.5%)	1 (4%)	4 (21%)	0 (0%)	
DORV	5 (8.5%)	2 (7%)	2 (10.5%)	1 (7%)	
TOF	4 (7%)	0 (0%)	4 (21%)	0 (0%)	
TOF-PA	2 (3%)	0 (0%)	2 (10.5%)	0 (0%)	
VSD	2 (3%)	0 (0%)	2 (10.5%)	0 (0%)	
DILV/DOLV	2 (3%)	2 (7%)	0 (0%)	0 (0%)	
PA-IVS	2 (3%)	0 (0%)	2 (10.5%)	0 (0%)	
Aortic valve disease	1 (2%)	0 (0%)	1 (5.5%)	0 (0%)	
HLHS	1 (2%)	1 (4%)	0 (0%)	0 (0%)	
Primary corrective surgery, n (%)					–
Fontan	18 (30%)	18 (67%)	0 (0%)	0 (0%)	
Bidirectional Glenn	11 (18%)	8 (30%)	3 (15.5%)	0 (0%)	
Atrial switch operation	7 (12%)	0 (0%)	0 (0%)	7 (50%)	
VSD closure	6 (10%)	0 (0%)	4 (21%)	2 (14%)	
TOF repair	4 (7%)	0 (0%)	4 (21%)	0 (0%)	
RVOTO repair (without conduit)	2 (3%)	0 (0%)	2 (10.5%)	0 (0%)	
RV-PA conduit	2 (3%)	0 (0%)	2 (10.5%)	0 (0%)	
Rastelli procedure	2 (3%)	0 (0%)	2 (10.5%)	0 (0%)	
Tricuspid valve surgery	2 (3%)	0 (0%)	1 (5.5%)	1 (7%)	
LV-PA conduit (ccTGA)	1 (2%)	0 (0%)	0 (0%)	1 (7%)	
Aortic valve surgery	1 (2%)	0 (0%)	1 (5.5%)	0 (0%)	
Banding PA	1 (2%)	1 (0%)	0 (0%)	0 (0%)	
Number of sternotomies	2 [1–3]	2 [2,3]	2 [2,3]	1 [1,2]	0.0012
Physiologic class*, n (%)					0.35
A	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
B	3 (5%)	3 (11%)	0 (0%)	0 (0%)	
C	45 (75%)	17 (63%)	16 (84%)	12 (86%)	
D	12 (20%)	7 (26%)	3 (16%)	2 (14%)	
Anatomical complexity*, n (%)					<0.001
Simple	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Moderate	11 (18%)	0 (0%)	11 (58%)	0 (0%)	
Great	49 (82%)	27 (100%)	8 (42%)	14 (100%)	
Medical therapy^, n (%)					–
ACE-I	32 (53%)	12 (44%)	11 (58%)	9 (64%)	
Beta-blocker	31 (52%)	11 (41%)	13 (68%)	7 (50%)	
Warfarin	31 (52%)	12 44%)	8 (42%)	11 (79%)	
Diuretics	30 (50%)	14 (52%)	9 (47%)	7 (50%)	
Digoxin	18 (30%)	7 (26%)	6 (32%)	5 (36%)	
Aspirin	17 (28%)	12 (44%)	1 (5.5%	4 (28%)	
Class I Anti-arrhythmic drug	12 (20%)	4 (14%)	6 (32%)	2 (14%)	
NOAC	4 (7%)	3 (11%)	0 (0%)	1 (7%)	
ARBs	3 (5%)	2 (7%)	1 (5.5%)	0 (0%)	
Statin	2 (3%)	1 (4%)	1 (5.5%)	0 (0%)	
Verapamil/Diltiazem	2 (3%)	0 (0%)	1 (5.5%)	1 (7%)	
Dihydropiridine CC-blocker	1 (1.5%)	0 (0%)	1 (5.5%)	1 (7%)	
PM, n (%)	10 (17%)	4 (15%)	3 (16%)	3 (21%)	0.91
ICD, n (%)	16 (27%)	1 (4%)	3 (42%)	7 (50%)	<0.001
ICD-CRT, n (%)	5 (8%)	0 (0%)	3 (16%)	2 (14%)	0.063
Systolic (systemic) ventricular function, n (%)					
Moderately reduced	30 (50%)	13 (48%)	9 (47%)	3 (22%)	0.89
Severely reduced	29 (49%)	8 (30%)	10 (53%)	11 (78%)	0.008
History of supraventricular arrhythmias, n (%)	38 (63%)	14 (52%)	13 (68%)	11 (79%)	0.23
History of ventricular arrhythmias, n (%)	7 (12%)	1 (4%)	4 (21%)	2 (14%)	0.27
Reason for heart transplant evaluation, n (%)					<0.001
Systemic ventricular dysfunction	28 (47%)	7 (26%)	10 (53%)	11 (79%)	
Advanced symptoms	17 (28%)	5 (19%)	9 (47%)	3 (21%)	
Fontan failure	12 (20%)	12 (44%)	0 (0%)	0 (0%)	
Progressive cyanosis	3 (5%)	3 (11%)	0 (0%)	0 (0%)	

ACE-I, Angiotensin-Converting Enzyme Inhibitor; ARBs, Angiotensin Receptor Blockers; BSA, Body Surface Area; cc; congenitally corrected; CC, Calcium Channel; D-, Dextro-; CRT, Cardiac Resynchronization Therapy; DILV, Double Inlet Left Ventricle; DOLV, Double Outlet Left Ventricle; DORV, Double Outlet Right Ventricle; HLHS, Hypoplastic Left Heart Syndrome; ICD, Implantable Cardioverter Defibrillator; LV, Left Ventricle; LV-PA, Left Ventricle to Pulmonary Artery; NYHA, New York Heart

Association Class; NOAC, Non-vitamin k antagonist Oral Anti-Coagulants; PA-IVS, Pulmonary Atresia with Intact Ventricular Septal Defect; PM, PaceMaker; RV, Right Ventricle; RVOTO, Right Ventricular Outflow Tract Obstruction; RV-PA, Right Ventricle to Pulmonary Artery; TGA, Transposition of the Great Arteries; TOF, Tetralogy of Fallot; TOF-PA, Tetralogy of Fallot with Pulmonary Atresia; VSD, Ventricular Septal Defect.

and cardiac imagers skilled in ACHD population and HTx.

According to the result of the multidisciplinary meeting the study population was then divided into:

- "Too well", patients without significant functional limitation and/or without a perceived survival advantage from transplantation;
- "Too bad", patients with poor clinical conditions or with overt contraindications for HTx excluded before carrying out HTx screening due to excess risk of mortality after transplantation;
- Accepted for screening.

HTx screening process has been reported elsewhere and it encompasses a standardized and comprehensive clinical, laboratory and instrumental evaluation (including cardiac catheterization) [11]. After HTx screening, decision process for HTx listing was made by the ACHD-HTx Heart Team. Screening results were defined as follows:

- "Screening failure" (HTx unsuitable due to excess risk of mortality after transplantation);
- "Patient refusal" (listed for HTx who refused to be listed for personal reasons);
- "Ongoing screening" (in screening at the time of the last follow-up);
- "Screening pass" (HTx suitable, standard risk of mortality after transplantation).

Primary study endpoint was failure to access HTx screening or listing at any decision node along the screening process for excess risk of mortality after transplantation.

Heart transplant, listing for HTx and mortality defined as all-cause mortality were evaluated as secondary outcomes.

CHD anatomical complexity was defined based on 32nd Bethesda conference [12].

CHD anatomical and physiological ACHD classification (class A through D) was assessed using definition of ACC/AHA ACHD 2018 Guidelines [13].

Renal disease was stratified and analyzed according to the CKD classification [14].

2.3. Statistical analyses

Between-group comparisons for clinical and outcome variables were performed using independent samples *t*-test, Wilcoxon rank sum test, chi-square analysis, or Fisher's exact test using appropriate variable-specific denominators.

Logistic regression modeling was used to compute hazard ratio (with 95% confidence interval) of the primary end point. A univariable logistic regression analysis was used to identify predictors of primary endpoint. Predictors achieving marginal significance (p value < 0.10) were entered in a multivariable logistic regression model. The final model retained (parsimonious approach) only variables with strong significance ($p < 0.05$) using stepwise backward selection.

An exploratory analysis assessed the relation between HTx refusal and overall mortality.

The time-to-event distribution was computed using Kaplan-Meier estimates accruing time of observation from the date of meeting evaluation. Univariable Cox modeling was used to compute hazard ratio (with 95% confidence interval) of mortality. Due to low number of observations multivariable analysis was not performed. A sensitivity analysis was performed excluding from the primary model patients transplanted before January 01, 2014 to account for the absence of patients refused from heart transplant during that period of time.

Data are reported as mean ± standard deviation, median (first and third quartile) or frequency (%).

All tests were two-sided. A p-value <0.05 was considered significant. Analysis was performed using STATA® 12th Release data analysis software (StataCorp LP, College Station, TX).

3. Results

3.1. Baseline characteristics

Between 2014 and 2020, a total of 3448 ACHD patients were evaluated in our Center; among them 46 (1.3%) ACHD patients were formally presented at the multidisciplinary ACHD-HTx conference with the specific goal of evaluation of HTx candidacy.

Fourteen ACHD patients underwent transplantation in the period between 2001 and 2013 and they were included in the study population.

Study final sample size was of 60 patients (Fig. 1).

Patients evaluated for HTx had a CHD of moderate or severe anatomic complexity (Table 1). All patients with univentricular heart and SRV had severe anatomic complexity by definition. Among 19 patients with SLV, 11 (58%) had moderate and 8 (42%) severe anatomic complexity (Table 1).

Overall, as expected, study population presented significant functional impairment in the majority of patients (29 patients [48%] had a history of NYHA class III or IV) without striking differences among ventricular morphology strata. Systolic function of the systemic ventricle was severely reduced in 8 (30%) patients with univentricular heart, in 10 (53%) with SLV and in 11 (78%) with SRV ($p = 0.008$).

Reason for discussion to candidacy to HTx was systemic ventricular dysfunction in 28 (47%) patients, presence of advanced symptoms in 17 (28%) patients, Fontan circulation failure in 12 (20%) patients and progressive cyanosis in 3 (5%) patients. The main indication in patients with SV was Fontan failure (44%), while in patients with SLV and SRV it was systemic ventricular dysfunction.

Additional clinical characteristics are shown in Table 1.

3.2. Multidisciplinary meeting results

Candidacy evaluation results are summarized in Fig. 1. At first evaluation 11 patients (30%) were excluded from screening for HTx for poor clinical conditions ("too bad"). Additional screening for heart transplantation was not performed in these patients.

In 32 of 46 patients (70%) screening was performed: at the last follow-up, 28 patients completed the screening, while for 4 patients screening was still ongoing.

After HTx screening, 4 patients were excluded (screening failure), 3 patients refused transplant for personal reasons and 21 patients were listed for HTx.

Of the patients in the waiting list, 7 are still on the active list, 4 died before HTx and 10 were transplanted (Fig. 1).

3.3. Clinical profile associated with candidacy status

We compared comorbidities and risk factors of the 41 patients considered suitable for transplantation (including both listed/transplanted patients, not yet listed because too well and patients who chose to refuse transplantation) and of the 15 patients refused after screening because of excess risk of mortality after transplantation (four patients with ongoing screening were excluded from this analysis) (Fig. 1).

Table 2 summarizes comparison of pertinent clinical variable in these two groups of patients. Details of patients excluded from HTx

Table 2
Comparison of pertinent clinical variables in patients refused from heart transplantation and residual cohort (without four patients with ongoing screening).

Variable	Overall cohort (n = 60)	Listed/patient refusal/HTx (n = 41)	Refused for heart transplant (n = 15)	p-value
CKD class, n (%)				0.16
I	33 (58%)	25 (61%)	7 (47%)	
II	16 (25%)	10 (24%)	4 (27%)	
III	8 (13%)	5 (12%)	2 (13%)	
IV	2 (4%)	0 (0%)	2 (13%)	
V	0 (0%)	0 (0%)	0 (0%)	
Liver disease, n (%)				0.63
Yes, no FALD	7 (11%)	4 (10%)	2 (13%)	
FALD	5 (9%)	3 (8%)	2 (13%)	
Protein-losing enteropathy, n (%)	3 (6%)	2 (5%)	1 (7%)	0.48
Refractory ascites, n (%)	13 (25%)	9 (22%)	4 (27%)	0.54
Obstructive lung disease, n (%)	4 (8%)	3 (7%)	1 (7%)	0.71
Restrictive lung disease, n (%)	9 (17%)	6 (15%)	3 (20%)	0.45
Severe scoliosis, n (%)	6 (11%)	3 (7%)	3 (20%)	0.19
History of stroke, n (%)	7 (13%)	4 (10%)	3 (20%)	0.27
Thyroid disease, n (%)	19 (34%)	15 (37%)	4 (27%)	0.36
Adverse anatomical features, n (%)	11 (21%)	3 (7%)	8 (53%)	<0.001
RA pressure, mmHg	10 [8–16]	9 [7–18]	12 [10–16]	0.18
Mean PA pressure, mmHg	19 [12–27]	19 [12–25]	24 [16–28]	0.30
PCW, mmHg	12 [8–17]	12 [7–17]	14 [11–18]	0.32
CI, L/m^2	2.3 (1.9–2.6)	2.3 (1.8–2.8)	2.2 (2.1–2.6)	0.96
TPG, mmHg	6 [4–9]	6 [4–8]	8 [4–12]	0.31
PVR, WU	1.6 (1.2–2.6)	1.5 (1.2–2.5)	2.1 (1–2.9)	0.72
Systemic EDVp, mmHg	10 [6–15]	9 [6–15]	12 [10–16]	0.08
INTERMACS class, n (%)				0.83
1	0 (0%)	0 (0%)	0 (0%)	
2	1 (2%)	1 (2.5%)	0 (0%)	
3	1 (2%)	1 (2.5%)	0 (0%)	
4	6 (10%)	4 (10%)	2 (13%)	
5	21 (36%)	15 (37%)	5 (33%)	
6	20 (34%)	14 (34%)	4 (27%)	
7	10 (17%)	5 (12%)	4 (27%)	
BUN, mg/dl	42 (35–66)	41 (34–58)	61 (37–73)	0.09
Creatinine, mg/dl	0.9 (0.8–1.3)	0.9 (0.8–1.1)	0.9 (0.8–1.3)	0.56
Total bilirubin, mg/dl	1.2 (0.6–1.7)	1.15 (0.6–1.5)	1.5 (0.7–2.0)	0.23
MELD score	13 [10–18]	13 [10–19]	13 [8–18]	0.63
MELD-XI score	11 [10–14]	11 [10–14]	13 [10–16]	0.30
Total protein, g/dl	7.2 (6.5–7.6)	6.9 (6.5–7.6)	7.5 (6.9–7.8)	0.11
Hemoglobin, g/dl	14.3 (12.1–16.5)	14.2 (11.9–16.9)	15.1 (12.4–17.1)	0.38
ABO Blood type, n (%)				0.47
0	23 (39%)	13 (32%)	8 (53%)	
A	26 (44%)	20 (49%)	5 (33%)	
B	7 (12%)	5 (12%)	2 (13%)	
AB	3 (5%)	2 (5%)	0 (0%)	
High titer PRA, n (%)	5 (19%)	3 (7%)	2 (15%)	0.09
Elevated PVR, n (%)	8 (14%)	4 (10%)	4 (27%)	0.12
Number of high-risk features, n (%)				0.012
0	23 (38%)	18 (44%)	3 (20%)	
1	14 (23%)	9 (22%)	3 (20%)	
2	8 (13%)	6 (15%)	2 (13%)	
3	10 (17%)	8 (20%)	2 (13%)	
4	3 (5%)	0 (0%)	3 (20%)	
5	2 (4%)	0 (0%)	2 (13%)	
Multiple (>2) high risk features, n (%)	15 (25%)	8 (19%)	7 (47%)	0.048^
Referred from non-HTx ACHD center, n (%)	19 (32%)	8 (20%)	9 (60%)	0.056
Systemic ventricle morphology, n (%)				0.63
Single ventricle	27 (45%)	17 (44%)	8 (53%)	
Anatomic left ventricle	19 (32%)	12 (32%)	6 (40%)	
Anatomic right ventricle	14 (24%)	9 (24%)	1 (7%)	

ACHD, Adult Congenital Heart Disease; BUN, Blood Urea Nitrogen; CKD, Chronic Kidney Disease; CI, Cardiac Index; EDVp, End Diastolic Ventricular pressure; FALD, Fontan-Associated Liver Disease; HTx, Heart Transplant; INTERMACS, INTERagency registry for Mechanically Assisted Circulatory Support; MELD, Model for End-stage Liver Disease; PA, Pulmonary Artery; PVR, Pulmonary Vascular Resistance; PCW, Pulmonary Capillary Wedge; PRA, Panel Reactivity Antibodies; RA, Right Atrium; TPG, TransPulmonary Gradient; -XI, eXcluding International normalized ratio.

evaluation are reported in Table 1 Online Supplementary Material.

No striking differences were noted between groups regarding CKD functional class, liver disease, presence of protein-losing enteropathy, refractory ascites, pulmonary obstructive or restrictive disease, severe scoliosis, history of stroke and thyroid disease (Table 2). Adverse anatomical features were significantly more common in patients refused from HTx compared to patients accepted for HTx evaluation (53% vs 7%, $p < 0.001$). Among these, severe scoliosis was present in 3 (7%) HTx-accepted and in 3 (20%) of HTx-refused patients. Adverse anatomical features were the only reason of exclusion in 4 patients.

Hemodynamic profile was similar between the two groups. INTERagency registry for Mechanically Assisted Circulatory Support (INTERMACS) class was somewhat preserved in the entire study population with only 2 patients (4%) with INTERMACS class below 4 and no major difference between declined and accepted HTx patients. Similarly, baseline laboratory profile did not suggest major difference regarding Blood Urea Nitrogen (BUN), creatinine, total bilirubin, Model for End Stage Liver Disease (MELD) and Model for End Stage Liver Disease –eXcluding INR (MELD-XI) score, total protein level, hemoglobin, ABO blood type and Panel Reactivity Antibodies titer.

The total number of high-risk factors was more prevalent in patients refused from HTx ($p = 0.012$).

Similarly, the presence of multiple risk factors (defined as > 2 concomitantly) was associated with exclusion from HTx ($p = 0.048$).

Referral pattern was significantly different between patients accepted or refused from HTx. Specifically, only eight (20%) of the 41 patients accepted and nine (60%) of 15 of the refused patients were referred from another Center.

Logistic regression analysis results are reported in Table 3. In the

Table 3
Risk factors associated to refusal from heart transplantation listing.

Variable	Univariable			Multivariable		
	OR	CI (95%)	p-value	OR	CI (95%)	p-value
Adverse anatomical features	14.5	3.1–68.4	0.001	14.4	1.2–171.7	0.035^
Systemic EDVp	1.09	0.96–1.23	0.21			
BUN	1.01	1.00–1.02	0.11			
High titer PRA	1.95	0.29–12.99	0.49			
Number of high-risk features	1.81	1.16–2.82	0.009			
Multiple (>2) high risk features	3.61	1.01–12.92	0.048^			
Referred from non-HTx ACHD center	5.3	1.50–19	0.01^	4.1	0.9–18.7	0.07^

ACHD, Adult Congenital Heart Disease; BUN, Blood Urea Nitrogen; EDVp, End Diastolic Ventricular pressure; HTx, Heart Transplant; OR, Odds Ratio; PRA, Panel Reactivity Antibodies.
^ $p > 0.05$ at the sensitivity analysis excluding HTx patients transplanted before January 01, 2014.

univariable analysis, adverse anatomical characteristics ($p = 0.001$), number of risk factors ($p = 0.009$), presence of multiple risk factors ($p = 0.048$) and the referral from another Center ($p = 0.01$) were associated to an increased risk of being refused from HTx. A sensitivity analysis carried out excluding patients transplanted before January 01, 2014 is reported in Table 3.

3.4. Characteristics of patients according to referral pattern

Within the 56 patients considered for the HTx-refusal analysis (excluding 4 patients with ongoing screening), 38 ACHD patients were evaluated in the setting of continuity of care within our Center, 18 were referred to our Center from another ACHD program specifically for HTx evaluation. Table 2 of the Online Supplementary Material reports pertinent comparison between these two groups of patients (patients with ongoing screening were not considered).

Patients referred from out-of-center ACHD program presented higher burden of non-cardiac comorbidities including renal disease, liver disease. Adverse anatomical features were more frequent among out-of-center referred patients (39% vs 10%, p 0.02). In addition cardiac profile was more compromised with higher right atrium (RA) pressure, marginally higher pulmonary artery (PA) pressure and higher pulmonary capillary wedge pressure (PCW).

Multiple risk factors were coexistent in 6 (16%) of the 38 patients in continuity of care in our Center, while in 9 (50%) of the 18 patients from another center ($p = 0.01$).

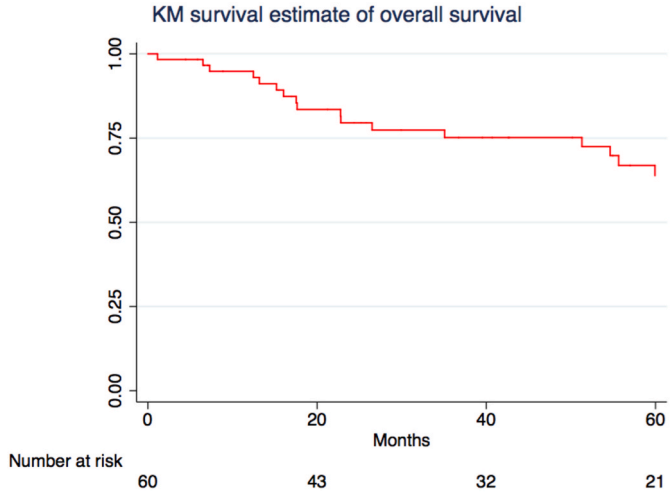

Fig. 2. Overall survival of patient cohort. Kaplan-Meier curve shows survival analysis of entire patient cohort.

3.5. Survival

During follow-up 18 out of 60 patients referred for transplant evaluation died and only one patient was lost to follow-up.

Deaths occurred in 3 of 11 patients considered "too bad" at the multidisciplinary meeting, in 4 patients refused from HTx screening because considered high risk, in 2 patients who refused HTx for personal reasons, in 4 patients on the waiting list and in 5 of the transplanted patients (Fig. 1).

Overall survival of entire the cohort considered at the multidisciplinary ACHD-HTX meeting at 20, 40 and 60 months was approximately 83%, 75% and 62%, respectively, as illustrated in Fig. 2.

Fig. 3 reports survival estimates in the 56 patients of the study population excluding 4 patients with ongoing screening at the time of data lock, differentiating those accepted or declined from HTx. We carried this analysis as per intention-to-treat approach, considering in the accepted for HTx both listed and transplanted patients and listed-only but not transplanted patients. Survival in patients accepted for HTx was significantly higher than survival in patients declined from HTx with landmark comparison at 20, 40 and 60 months of 87%, 78% and 72% vs. 70%, 59% and 20% respectively.

The elapsed time between the MDM and the HTx for listed patients who underwent transplantation and the time elapsed between MDM and the death for declined from HTx was then compared. Such comparison showed some overlap with time to transplant (in the HTx listed and transplanted patients) of the same magnitude of time to death (in the declined from HTx patients) (Fig. 4).

4. Discussion

HF burden, morbidity and mortality in ACHD patients are the inevitable trade-off of increasing survival and complexity of patients born with CHD [15]. The number of hospitalization for HF in ACHD patients is increasing and HF is the current leading cause of death in the ACHD population [4].

HTx has been increasingly reported in ACHD patients with end-stage HF [16]. Implementation of HTx in this population has been challenging for a number of ACHD-related features. HF presentation in ACHD is often diverse and peculiar compared to non-ACHD population [15]. ACHD patients present significant heterogeneity in the anatomy and pathophysiology serving as background substrate of HF in ACHD [8]. Moreover, identification of high-risk ACHD patients with HF remains elusive due to the lack of longitudinal outcome data in large cohorts. Furthermore, landmark clinical trials in HF have usually excluded patient with CHD [10].

As a consequence, listing for HTx remains a challenging task in ACHD cardiovascular medicine. European practice toward candidacy status for ACHD patients is not uniform [17]. Similar to other countries, including United States of America, CHD do usually convey a lower status compared to other cardiac disease and ACHD patients are usually listed along with patients with non-congenital heart disease. Converging data suggest that ACHD patients are often listed too late, experience higher than expected waitlist mortality or delisting due to deterioration and are often listed at a lower status that non-ACHD patients [10, 18–21].

Dissecting HTx candidacy decision-making process appears to be relevant to increase access to HTx for ACHD patients, reducing waitlist mortality, and improve patient outcome.

Our study adds some insights to this regard: a) ~1.5% of consecutive

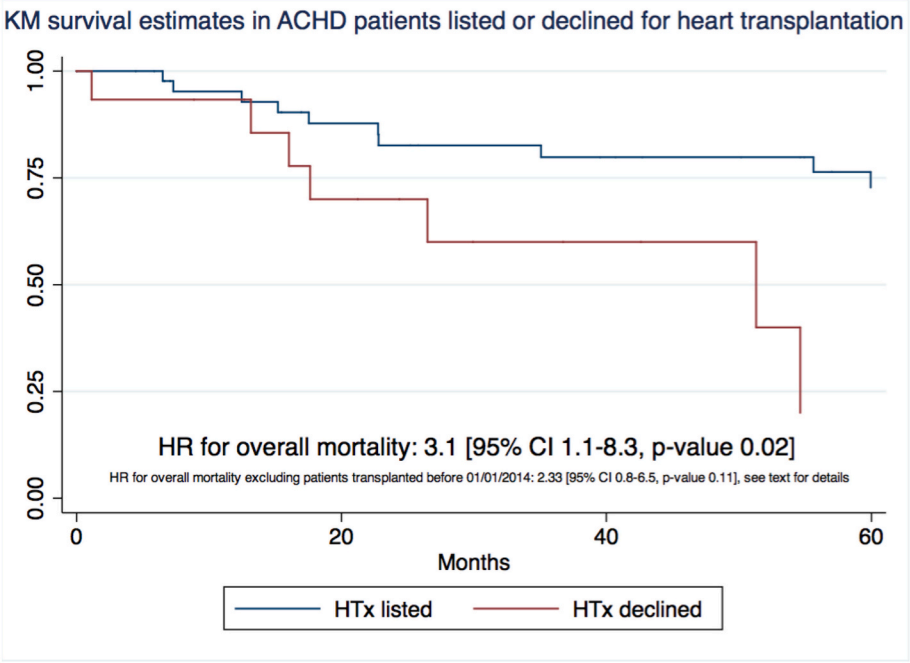

Fig. 3. Comparison of survival between patients listed and declined for heart transplant. Kaplan-Meier curves. Intention-to-treat analysis carried out in the 56 study patients excluding 4 patients with ongoing screening at the time of data lock: Patients listed for heart transplant [HTx listed, in blue] encompass both patients listed and heart-transplanted and patients listed but not transplanted; patients refused for heart transplant [HTx declined] are depicted in red. The cumulative area between the curves, at each time point, represents the life span gain from the time of multidisciplinary meeting. A sensitivity analysis has been carried out excluding patients transplanted before January 1st, 2014. CI= Confidence Interval; HR= Hazard Ratio; HTx = Heart transplant.

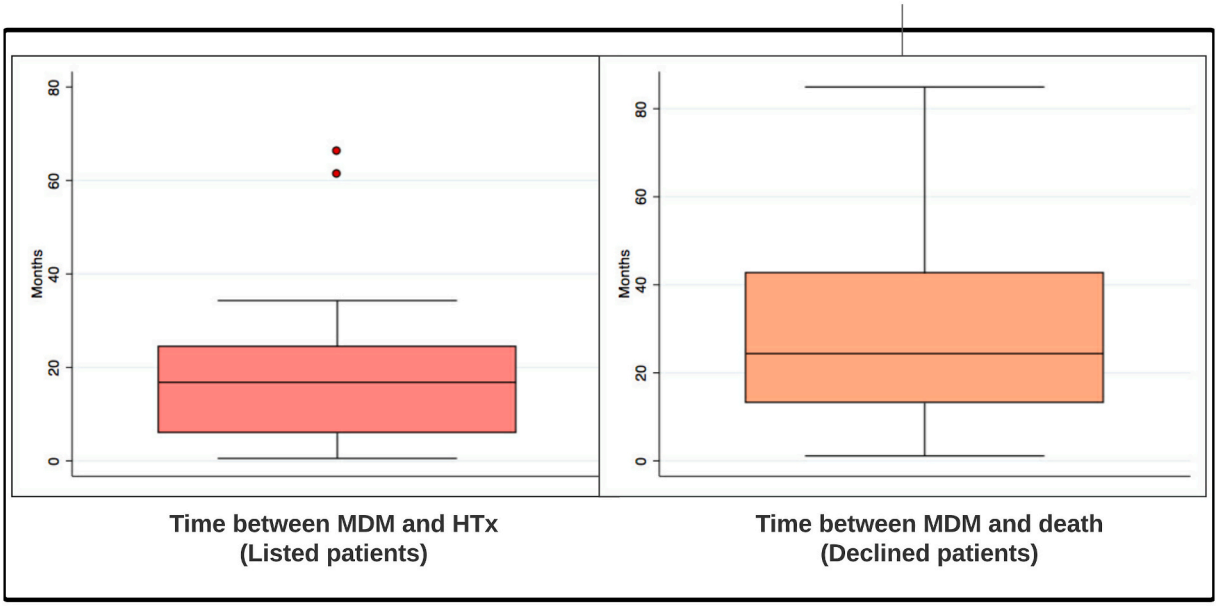

Fig. 4. Time interval between multidisciplinary meeting and outcomes. Comparison between time elapse between multidisciplinary meeting and orthotopic heart transplant (in listed patients) or death (in declined patients). HTx = Heart transplant; MDM = multidisciplinary meeting.

ACHD patients have been referred for HTx evaluation over a 7 year period in a tertiary ACHD/HTx referral center; b) candidacy for HTx is refused to almost 40% of ACHD patients referred for HTx evaluation during study period; c) risk factors for refusal are simultaneous presence of conventional high risk features, anatomical factors, out-of-center ACHD/HTx program referral; d) HTx refusal identify a very high risk ACHD patient subgroup with shorter time to death, irrespective of HTx surgery in the accepted-for-HTx subgroup.

HTx listing is a delicate clinical decision that must consider and account for potentially conflicting elements such as graft survival, waitlist mortality, patient-specific gain of survival with transplantation (Fig. 5) [22]. Transplantation medicine is plagued by chronic scarcity of donors with growing offer-demand mismatch and competitive access to candidacy between ACHD and non-ACHD patients is inevitable. Non-ACHD patients are usually listed with higher status compared to ACHD population [10]. Differential status between these two patient populations is resulting from a variety of factors including specifics of HF presentation and marginal access to mechanical circulatory support (MCS) in the ACHD population (in particular in patients with Fontan circulation or very complex CHD) [23].

Our data provide evidence that HTx access in ACHD patients is jeopardized by two different groups of risk factors: a) lesion/anatomic specific factor (largely time-independent), including thoracic deformity with severe scoliosis and restrictive lung disease; b) time-dependent factors including renal/hepatic dysfunction, obesity, pulmonary vascular disease. In addition, in our experience, patient referred for HTx

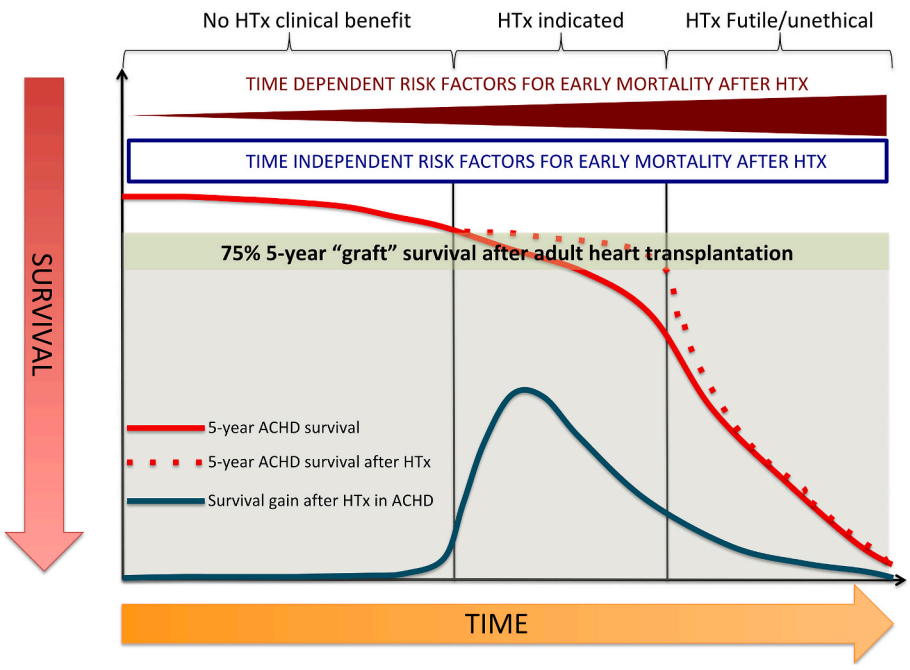

Fig. 5. Graphical summary of the interplay between time-independent and time-dependent risk factors for early mortality after HTx with ACHD disease course. Ideally, the indication to HTx must take into account "graft" survival (for ethical consideration) and patient survival. The shaded green area denotes the current 5-year survival rate after adult heart transplantation (ideal graft survival). A hypothetical three-stages trajectory of ACHD natural course is presented (red line). If the individual patient 5-year survival is above the ideal graft survival, HTx is not clinically justified. When 5-year survival rate drops below the ideal graft survival a window of opportunity for proper HTx referral unfolds. During this phase there is a potential significant survival gain if the patient undergoes HTx (green line and dashed red line). With progression of the disease the individual 5-year survival rate is significantly reduced and the increase in HTx-mortality portends poor survival gain after transplantation (dashed red line approaching un-dashed red line), as a consequence the individual ACHD patient survival after HTx would be significantly lower the ideal graft survival adding ethical concerns to clinical futility. ACHD = Adult Congenital Heart Disease; HTx = Heart Transplantation.

evaluation to our Center from other non HTx/ACHD Centers had greater chance of being refused from HTx for coexistence of multiple high-risk features.

ACHD cardiovascular medicine has emerged and matured over the past few decades as a sub-specialty field of modern cardiology [24]. End-stage HF and transplantation in ACHD remains a controversial field where specific expertise in HTx evaluation is required to enhance listing timing and to ensure the best chance for successful screening process to ACHD patients. Multicenter studies are required to identify ACHD patients with higher propensity for developing end-stage HF and test the hypothesis that early referral to ACHD/HTx Center is able to increase the chance for successful screening and listing.

The overlap between time to death in refused to HTx patients and time to transplantation in the accepted for HTx patients may indirectly suggest that even if we chose to list refused patients, these would likely have died in the waitlist before transplantation.

Our data reinforce the importance of large multicenter studies specifically devoted to this topic to better define risk factors for early mortality after transplantation or during waitlist, to explore potential use of MCS as a measure to rescue "sicker" patients before transplantation, to delineate proper timing for referral and overall increase appropriate listing and choice of listing status [25–28].

In our study HTx refusal portends shorter time to death irrespective to HTx surgery. Delisting due to deterioration is known risk factor for early death in ACHD [29]. Our study design is not suitable to assess the HTx-related survival gain in ACHD, but it must be emphasized that in ACHD patients referred for HTx and refused from listing, an open discussion must occur. Such discussion should address end-of-life consideration and should prompt to explore any potential need for palliative care and redirection of care to ensure dignity and appropriate support to patient and family [30].

4.1. Study limitations

Our study is not without limitations. First, this research was conducted in a single Center with a relatively small number of patients, even if our institution is the regional coordinating center for HTx and ACHD in our region. Our data must be confirmed in a multicenter study specifically designed to capture and describe candidacy evaluation in ACHD.

Some clinical or laboratory data at baseline and during follow-up are missing due to inability to gain full access to clinical reports before 2014. Finally, patients transplanted before January 01, 2014 were included even if the absence of patients refused from heart transplant during that period of time. However, it should be noted that HTx screening and evaluation practice has not changed in our Institution recently. As a consequence, it is unlikely that informative selection bias has occurred including patients transplanted before 2014. This statement is reinforced by direct comparison of patients transplanted before and after 2014 as reported in Table 3 of the Online Supplementary Material. This comparison confirms that the "historical" HTx cohort and the "inception" HTx cohort are similar with regards of most clinical features and baseline demographics, suggesting that no major clinical shiftingin HTx cohort composition has occurred.

Larger and presumably multicenter studies with higher number of patients are required for confirmation of our study findings and to dissect whether HTx candidacy may be improved by selected clinical strategies.

5. Conclusions

HTx referral screening and listing is poorly defined in ACHD. These patients experience excess waitlist mortality or delisting due to deterioration. Our study confirms that candidacy in ACHD population is limited with 40% of ACHD patients referred for HTx evaluation are ultimately declined. Risk factors for refusal are anatomical factors, multiple and simultaneous high-risk factors and out-of-center referral. ACHD patients refused from HTx present shorter time to death compared to patients accepted for HTx irrespective of HTx surgery. Additional, large, multicenter studies are needed to confirm these results and to identify strategies to increase candidacy, reducing waitlist mortality, and to improve outcomes in this growing population of patients.

Contributorship statement

Study planning: E.A., E.C.D., G.E.A., L.P., A.D., G.D.G. Study conduct: E.C.D., F.T., R.Z., F.D.P., L.C., Y.B., C.C., A.B. Study reporting: E.A., E.C.D., G.E.A., L.P., A.D., G.D.G. Study guarantor(s): G.E.A, E.A.

Declaration of competing interest

No authors report any relevant conflict of interest regarding this manuscript.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcchd.2022.100363.

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Abbreviations

AI: artificial intelligence
ACHD: adult with congenital heart disease
BSA: body surface area
BUN: Blood Urea Nitrogen
ccTGA: congenitally corrected transposition of the great arteries
CHD: congenital heart disease
ICD: implantable cardioverter defibrillator
FALD: fontan-associated liver disease
HF: heart failure
HLA: human leukocyte antigens
HLHS: hypoplastic left heart syndrome
HTx: heart transplant
INTERMACS: INTERagency registry for Mechanically Assisted Circulatory Support
MELD: Model for End Stage Liver Disease
MELD-XI: Model for End Stage Liver Disease –eXcluding INR
MDM: = multidisciplinary meeting
mPAP: mean pulmonary arterial pressure
PRA: panel reactivity antibodies
PVR: pulmonary vascular resistances
RAP: right atrial pressure
SV: single ventricle
SLV: systemic left ventricle
SRV: right systemic ventricle
TGA: transposition of great arteries
WU: wood units